

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 November 2001 (08.11.2001)

PCT

(10) International Publication Number
WO 01/82880 A2

(51) International Patent Classification⁷: **A61K 7/06**

(21) International Application Number: **PCT/US01/13900**

(22) International Filing Date: 30 April 2001 (30.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/563,555 3 May 2000 (03.05.2000) US

(81) Designated States (*national*): AE, AG, A1, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FL, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant and
(72) Inventor: **GOODMAN, David, S. [US/US]; 721 Wood-haven Lane, Naples, FL 34108 (US).**

(74) Agent: **PEARLMAN, Robert, I.; Riker, Danzig, Scherer, Hyland & Perretti LLP, Headquarters Plaza, One Speedwell Avenue, Morristown, NJ 07962 (US).**

Published:
— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/82880 A2

(54) Title: TOPICAL PREPARATION FOR THE TREATMENT OF HAIR LOSS

(57) Abstract: Improved preparations for the treatment of androgenetic alopecia comprise saw palmetto berry extract containing phytosterols and one or more low irritability constituents that enhance penetration of the extract into hair follicular pores. The low irritability penetration enhancer(s) may be selected from the group consisting of adapalene, tretinoin, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid. Also provided is a method for reducing hair loss by application to the scalp of the improved preparations.

TOPICAL PREPARATION FOR THE TREATMENT OF HAIR LOSS

5

BACKGROUND OF THE INVENTION**1. Field of the Invention**

This invention relates to an improved preparation and method for treating androgenetic alopecia; and more particularly to a preparation comprising an active extract of saw palmetto berries and a compound which exhibits low irritability and enhances penetration of the extract into hair follicular pores.

2. Description of the Prior Art

Human hair undergoes a normal growth cycle, known as the pilar cycle where each hair grows continuously for about 2 to 4 years, stops growing for 2 to 4 months, and then falls out. In its place, healthy new hair begins to grow, thereby restarting the cycle. Androgen receptors located in the hair follicle and sebaceous gland sensitize hair follicles to androgens. There is evidence that the pilar cycle of hair follicles on the scalp respond to higher levels of androgens by displaying shortened growth phases, and by displaying a greater fraction of increasingly thinner and shorter hairs.

Saw palmetto (*serenoa repens*) is a small berry-bearing palm native to the southeast United States. Saw palmetto berry extract ("SPBE") has been shown to block 5-alpha reductase, the enzyme that converts the hormone testosterone into dihydrotestosterone ("DHT"), the major androgen implicated in changes in the pilar cycle. This enzyme also blocks the binding of DHT to androgen receptors. Thus, in treating the balding scalp, SPBE may act by blocking the formation of DHT, by inhibiting binding of DHT to the androgen receptors, or both. The use of SPBE in

reducing hair loss is well known and has been cited for ex:

Pharmacy, pp.78-79, Rodale Press, Emmaus, PA, 1996

In U.S. Patent 5,972,345, SPBE has been combined with the extracts of African Pygeum and stinging nettle to produce a formulation for administration to the 5 scalp for the treatment of male pattern hair loss. Stinging nettle extract is a known rubefacient that may open the follicle entrance by producing irritation.

In U.S. Patent 5,750,108, SPBE is administered to the scalp as the third step in a procedure comprising lengthy, sequential preparatory treatments, first with tea tree oil, and then with an acidic solution of chlorine dioxide. The purpose of these 10 preparatory treatments is to remove sebum from the follicle entrance and improve the effectiveness of the SBPE. However, chlorine dioxide is an irritant and an extremely hazardous material. The Occupational Safety and Health Administration of the U.S. Department of Labor, in a list published by Government Institutes, Inc. Rockville, MD, 1990, shows a Permissible Exposure Level (PEL) for chlorine dioxide vapor as 15 0.1 ppm. To understand this level of toxicity, it should be noted that elemental chlorine that has been used as a war gas, has a PEL that is five fold greater than that of chlorine dioxide.

SPBE has also been disclosed in U.S. Patent Nos. 5,624,673, 5,653,983, and 5663,160 as an optional minor ingredient in topical formulations.

20 Other known topical formulations for treatment of hair loss are minoxidil, and a combination of minoxidil with tretinoin. The efficacy of minoxidil is limited as only a relatively small percentage of patients using it develop mild to moderate regrowth of hair. Further, Pharmacia and Upjohn, manufacturers of ROGAINE® minoxidil solution, warn that the most common side effect of minoxidil is itching 25 and skin irritation of the treated area of the scalp. Tretinoin may also act as an irritant

as indicated by the publication "Topical Tretinoin in Acne
Webster, Journal of the American Academy of Dermatology, S38-S43, (1998).

A need exists for an SPBE formulation and method of preventing hair loss/promoting hair growth that exploits the merits of SPBE without requiring lengthy 5 and hazardous pretreatment of the scalp. Especially needed is an SPBE formulation that offers enhanced effectiveness without causing scalp irritation.

SUMMARY OF THE INVENTION

The invention provides an improved preparation and a method for treating 10 androgenetic alopecia. The preparation comprises an extract of saw palmetto berries containing phytosterols and a non-irritating compound to enhance the penetration of the extract into the follicles. More specifically, the improved low irritability topical preparation comprises saw palmetto berry extract containing phytosterols and one or more penetration enhancing constituents selected from the group consisting of 15 adapalene, tretinoin gel microsponges, tretinoin and polyolprepolymer-2, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid. Preferably the penetration enhancing constituents consist of one member selected from the group consisting of adapalene, tretinoin and polyolprepolymer-2, and tretinoin gel microsponges, and another member selected from the group consisting of salicylic 20 acid and glycolic acid.

In another embodiment, the improved low irritability topical preparation comprises an active saw palmetto berry extract containing phytosterols, polyolprepolymer-2 and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin, retinaldehyde, tazarotene, salicylic acid, 25 azelaic acid, and glycolic acid. Preferably the penetration enhancing constituents

consist of one member selected from the group consisting of a
and another member selected from the group consisting of salicylic acid and glycolic
acid.

Most preferably, in both of the above embodiments, the penetration
5 enhancing constituents are adapalene and glycolic acid.

The preparations of the invention may include a vehicle suitable for topical application to the scalp in the form of a liquid, a gel, a foam, a styling hair tonic, a styling mousse, a styling hair spray, a pad damped with a liquid, or any other means suitable for application to the scalp.

10 The method for the treatment of androgenetic alopecia comprises applying to the scalp a low irritability preparation comprising saw palmetto berry extract containing phytosterols, and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin gel microsponges, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid. In another embodiment, the
15 method for the treatment of androgenetic alopecia comprises applying to the scalp a low irritability preparation comprising saw palmetto berry extract containing phytosterols, polyolprepolymer-2 and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid.

20

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides low irritability formulations of SPBE offering enhanced effectiveness in reducing hair loss by their greater ability to penetrate the pores of the scalp. In addition, there is provided by the invention a

method for reducing hair loss by application to the scalp of a pre
the improved formulations.

The pilar cycle in humans is measured in years, typically two to four years.
Consequently, a topical preparation to be effective in reducing hair loss or promoting
5 hair growth must be used for extended periods of time. It is evident that a preparation
or a method that causes irritation of the scalp often cannot be used for the time
essential to be effective.

The SPBE constituent of the preparation of the invention may be obtained
from a number of commercial sources. Satisfactory non-irritating SPBEs include
10 Permixon® from P.F. Médicaments, Paris, France, SPBE from McZand Herbal Inc.,
Santa Monica, CA, and others.

In a preferred embodiment of the preparation of the present invention, the
SPBE constituent is the alcohol soluble material sold by Saw Palmetto Harvesting
Company, Frostproof FL. This SPBE is non-irritating when applied to the scalp.
15 Typically, it has the following major components and concentrations:

Phytosterols

	capesteryl	about 0.01 to about 0.1 wt.wt.%
	beta-sitosterol	about 0.1 to about 0.4 wt.%
	stigmastanol	about 0.01 to about 0.1 wt.%
20	Total sterols	greater than about 0.15 wt.%

Fatty Acids

	caprylic	about 1.0 to about 3.0 wt.%
	capric	about 1.0 to about 3.0 wt.%
	lauric	about 25 to about 32 wt.%
25	cis-linoleic	about 3.0 to about 5.0 wt.%

	linolenic	about 0.5 to about 1.5 wt.%
	myristic	about 10 to about 15 wt.%
	oleic	about 26 to about 35 wt.%
	palmitic	about 7 to about 11 wt.%
5	stearic	about 1.0 to about 2.0 wt.%

Other phytosterols, other fatty acids and other minor components may also be present without effecting the utility of the SPBE. The phytosterols are believed to be the active agents in the SPBE.

In another embodiment of the preparation of the present invention, all or a portion of the fatty acids have been removed from the above composition by further purification, as for example by extraction with aqueous alkaline solution. In this embodiment, the phytosterol composition of the SPBE is as follows:

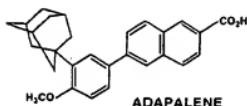
<u>Phytosterols</u>		
	capesterol	greater than about 0.02 wt.%
15	beta-sitosterol	greater than about 0.2 wt.%
	stigmastanol	greater than about 0.02 wt.%
	Total sterols	greater than about 0.3 wt.%

The SPBE is present in the preparations of the invention in a concentration such that the concentration of phytosterols in the total preparation is between about 0.01 wt.% and 1 wt.%. Preferably, the concentration of the SPBE is such that the concentration of the phytosterols in the total preparation is between about 0.01 wt.% and 0.5 wt.%. Most preferably the phytosterol concentration is about 0.10 wt.%.

The preparation of the invention comprises the SPBE and one or more penetration enhancing constituents selected from the group consisting of adapalene,

tretinoin gel microsponges, retinaldehyde, tazarotene, salicylic acid, glycolic acid. In another embodiment, the preparation of the invention comprises the SPBE, polyol prepolymer-2 and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin, retinaldehyde, tazarotene, 5 salicylic acid, azelaic acid, and glycolic acid.

Adapalene is a synthetic retinoid manufactured by Galderma having the following structural formula:

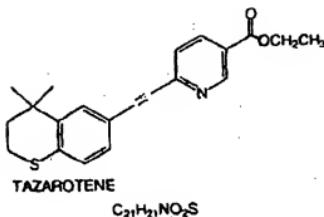


A research article by B. Shroot, "Pharmacodynamics and Pharmacokinetics of Topical Adapalene", Journal of the American Academy of Dermatology, S17-S24, (1998) has shown that adapalene has several useful properties. First, adapalene has significant comedolytic activity, that is, it opens comedones or clogged pores. In the preparation of the invention, adapalene acts to enhance the effectiveness of the SPBE. Second, a 0.1 wt.% adapalene gel has a low irritative potential only slightly greater than a petroleum jelly control. Third, 15 adapalene has anti-inflammatory effects both in vitro and in vivo. Each of these documented properties provides superiority to the preparations of the invention over the SPBE formulations of the prior art. Lastly, as adapalene is a retinoid, it may be expected to have direct benefits on stimulating hair growth.

Adapalene is present in a preparation of the invention in a concentration 20 from about 0.01 wt.% to about 1 wt %. Preferably, the adapalene concentration is from

about 0.05 wt.% to about 0.5 wt.%. Most preferably, the adap
about 0.1wt.%.

Tazarotene is a retinoid having the following structural formula:



Pharmacologically, tazarotene normalizes keratinocyte differentiation and minimizes proliferation of keratinocytes. These actions serve to inhibit microcomedo formation and prevent follicular plugging. Tazarotene also decreases epidermal inflammation and has been shown to down-regulate biochemical markers of inflammation. In the preparation of the invention, tazarotene acts to enhance the effectiveness of the SPBE.

Tazarotene is present in a preparation of the invention in a concentration from about 0.01wt.% to about 1wt%. Preferably, the tazarotene concentration is from about 0.02 wt.% to about 0.2 wt%. Most preferably, the tazarotene concentration is about 0.05 to 0.1 wt%.

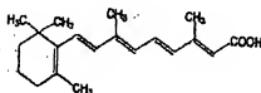
Glycolic acid, a naturally occurring α -hydroxy acid has the formula:



Glycolic acid been shown to exfoliate the stratum

preparation of the invention, glycolic acid acts to enhance the effectiveness of the SPBE by increasing its penetration. Additionally, a research article by N.V. Perricone et al, "Photoprotective and Anti-inflammatory Effects of Topical Glycolic Acid",
5 Dermatological Surgery, 22, 435-437 (1996) has shown glycolic acid acts as both a photoprotective agent and as an anti-inflammatory. These photoprotective and anti-inflammatory properties lend superiority to the preparations of the invention over the SPBE formulations of the prior art. Glycolic acid is present in a preparation of the invention in a concentration from about 0.1 wt.% to about 20 wt %. Preferably, the
10 glycolic acid concentration is from about 0.5 wt.% to about 10 wt %. Most preferably, the glycolic acid concentration is about 5 wt %.

Tretinoin has been used in acne therapy and in combination with minoxidil for the prevention of hair loss. Tretinoin is all-trans retinoic acid, also known as (all E) 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8,-
15 nonatetraenoic acid having the following structural formula:



20 Tretinoin inhibits comedo formation and enhances comedolysis. Thus, it acts to prevent pores from becoming clogged and enhances removal of debris from clogged pores. There is also evidence that tretinoin itself increases hair growth factors. Additionally, a new form of topical tretinoin, RETIN-A MICRO®, has become available from Ortho Dermatological, Raritan N.J. in which 0.1wt.% of
25 tretinoin is entrapped in a microscopic particle termed a "microsponge". This

particle localizes to the follicle after topical application and the slow release minimizes irritation. By virtue of their increased effectiveness and low irritation potential, a preparation of the invention containing tretinoin in the form of gel microsponges is superior to SPBE preparations of the prior art. Tretinoin is present in a preparation of the invention in a concentration from about 0.005 wt.% to about 0.2 wt.%. Preferably tretinoin concentration is from about 0.025 wt.% to about 0.1 wt.%.

Retinaldehyde is the aldehyde analog of retinoic acid having a terminal aldehyde group in place of the carboxyl group of retinoic acid. It has been shown by 10 J.W. Fluhr et al, Dermatology, 199, Suppl 1:57-60 (1999) that retinaldehyde is significantly less irritating than retinoic acid (tretinoin). It is expected to be equally as effective in increasing the absorption of SPBE as is tretinoin. Incorporation of retinaldehyde in the SPBE preparations of the invention provides superior effectiveness and lower irritation potential of these preparations over the SPBE 15 formulations of the prior art. Retinaldehyde is present in a preparation of the invention in a concentration from about 0.01wt.% to about 1.0 wt.%. Preferably the retinaldehyde concentration is from about 0.05 wt.% to about 0.5wt.%. Most preferably, the retinaldehyde concentration is about 0.1wt.%.

Azelaic acid, also known as 1,7 heptanedicarboxylic acid has the formula: 20 HOOC-(CH₂)₇-COOH
This agent has been shown to have antibacterial, antikeratinizing and anti-inflammatory properties. Thus, its use leads to a reduction in thickness of the stratum corneum or top layers of the skin, while preventing the formation of microcomedones or plugged follicles. These effects allow for increased penetration 25 of SPBE into follicles while causing little, if any, irritation. Azelaic acid has been

shown to cause less irritation than tretinoin. Incorporation of aze preparations of the invention provides superior effectiveness and lower irritation potential of these preparations over the SPBE formulations of the prior art.

Azeleic acid is present in a preparation of the invention in a concentration 5 from about 0.1 wt.% to about 40 wt%. Preferably, the azeleic acid concentration is about 20 wt.%.

It has been shown by M.C. Spellman et al, Clinical Therapy, 20(4), 711-721 (1998) that a combination of azelaic acid and glycolic acid is less irritating than tretinoin and equally as effective in treating facial acne. As both azeleic acid and 10 glycolic acid lead to a reduction in the thickness of the stratum corneum, and both have anti-inflammatory properties, this combination increases the absorption of topically applied SPBE while causing less irritation than prior art compounds. Accordingly, incorporation of azelaic acid and glycolic acid in the SPBE preparations 15 of the invention provides superiority of these preparations over prior art SPBE formulations.

Azelaic and glycolic acids are present in a preparation of the invention in relative proportions ranging from about 10:90 azelaic:glycolic to about 90:10 azelaic:glycolic. The total concentration of azelaic plus glycolic acids in a preparation of the invention is from about 0.1 wt.% to about 40 wt%. Preferably, the azelaic plus 20 glycolic acid concentration is about 20 wt%.

Salicylic acid (2-hydroxy benzoic acid) is a beta hydroxy acid having the formula:



Salicylic acid is used topically in numerous products to reduce scaling. It 25 is well known as a keratolytic and has been used in combination with glycolic acid to

aid in comedolysis or the opening of clogged follicles. It increases SPBE into follicles and has a low irritancy potential. Incorporation of salicylic acid in the SPBE preparations of the invention provides superiority of these preparations over the SPBE formulations of the prior art.

5 Salicylic acid is present in a preparation of the invention in a concentration from about 0.1 wt.% to about 10 wt.%. Preferably, the salicylic concentration is between about 1% wt.% and 3 wt.%.

Polyol prepolymer-2 is a urethane compound of molecular weight up to about 200,000 which is prepared by reacting approximately two moles of a hydroxy 10 terminated linear alkylene or polyalkylene glycol or polyether with approximately one mole of a monomeric organic diisocyanate as described in U.S. Patent 5,700,483, the entirety of which is incorporated by reference herein. Preferably, polyol prepolymer-2 has average molecular weight of about 4000 and is prepared by reacting about one mole of dicyclohexylmethanediisocyanate with about two moles of propylene glycol
15 725.

Incorporation of polyol prepolymer-2 in a topical formulation has been shown to have the characteristic of moderating the rate of transmission of a retinoid to the skin. Specifically, it has been shown that formulations incorporating tretinoin and polyol prepolymer-2 are significantly less irritating and exhibit therapeutically equally 20 efficacy to identical formulations without polyol prepolymer-2. When polyol prepolymer-2 is present in a preparation of the invention, tretinoin need not be in the form of gel microsponges. Incorporation of the polyol prepolymer-2 in the SPBE preparations of the invention provides superiority of these preparations over the SPBE formulations of the prior art. The polyol prepolymer-2 is present in a 25 preparation of the invention in a concentration from about 1 wt% to about 20 wt%.

Preferably, the polyol prepolymer-2 is present in a concentration about 15 wt%.

The preparations of the invention may include a vehicle for the application to the scalp such as a liquid, a gel, a foam, a styling mouse, a styling gel, a styling hair 5 tonic, a styling hair spray a lotion, a pad dampened with a liquid, or any other means suitable for application to the scalp. Preferably the SPBE preparations of the invention are employed as a liquid or as a gel. Most preferred is a gel.

The formulation of all such topical vehicles is well known to those skilled in the art. A suitable topical vehicle for formulation of the SPBE preparation as a 10 liquid includes ethanol, isopropanol, their mixtures in all proportions. To prepare a liquid preparation of the invention, the SPBE and the penetration enhancing constituents are dissolved or dispersed in the alcohol constituents with agitation. Elevated temperatures may be used to facilitate the dispersion process.

An example of a suitable topical vehicle for formulation of the SPBE 15 preparation as a gel is:

<u>Component</u>	<u>wt%</u>
hydroxypropylcellulose	2.1
70/30 isopropyl alcohol/water	90.9
propylene glycol	5.1
20 Polysorbate 80	1.9

To prepare a gel preparation of the invention, the 70% isopropanol and the propylene glycol are first combined. The SPBE and the penetration enhancing constituents are dispersed in the alcohols with agitation. The hydroxypropylcellulose 25 and the Polysorbate 80 are then incorporated with mixing until a gel results.

An example of a suitable topical vehicle formulation

SPBE preparation as a foam is:

<u>Component</u>	<u>wt%</u>
cetyl alcohol	1.1
5 stearyl alcohol	0.5
Quaternium 52 (52%)	1.0
propylene glycol	2.0
Ethanol 95 PGF3	61.05
deionized water	30.05
10 P75 hydrocarbon propellant	4.30

To prepare a foam preparation of the invention, the SPBE and the penetration enhancing constituents are first dispersed in the ethanol at elevated temperature. The cetyl and stearyl alcohols are added to the heated dispersion and mixed until dissolved. The Quaternium 52, the propylene glycol and water are added 15 and stirred until homogeneous while maintaining elevated temperature. The mixture is cooled and dispensed into an aerosol can. A valve is fitted to the can and the can is then charged with the propellant.

A suitable topical vehicle for formulation of the SPBE preparation as a hair grooming tonic is the formulation of Example VI of U.S. Patent 5,997,853, the 20 entirety of which is incorporated by reference herein. The SPBE and the penetration enhancing constituents are first incorporated in the ethanol constituent and the remaining components are added and incorporated by mixing together in a conventional manner.

A suitable topical vehicle for formulation of the SPBE preparation as a 25 styling mousse is the formulation of Example XIII of U.S. Patent 5,997,853. The

SPBE and the penetration enhancing constituents are first incorporated in the ethanol. Then, the remaining components except the isobutane are added, and blended together at ambient temperature until well mixed. Aluminum aerosol cans are filled with 95 parts of this batch, a valve is fitted to the can and lastly pressure is applied to the can to fill it with 5 parts isobutane.

A suitable topical vehicle for formulation of the SPBE preparation as a styling hair spray is the formulation of Example XIV of U.S. Patent 5,997,853. The SPBE and the penetration enhancing constituents are first incorporated in the ethanol. The remaining ingredients are then added and mixed in a conventional manner.

10 The mode of use of a SPBE preparation of the invention is application of 1 cc of the preparation to the affected area of the dry scalp twice a day for a period of four months. The preparation should be massaged into the scalp and remain in place for at least four hours before washing, rinsing or showering. After the four month initial period, a sustaining application of 1 cc once a day is used.

15 The following examples are presented to provide a more complete understanding of the invention. The specific techniques, conditions, materials, and proportions set forth to illustrate the principles and practice of the invention are exemplary and should not be construed as limiting the scope of the invention.

20

EXAMPLES

Examples I-14

Tables I and II below provide examples of preparations of the invention. The SPBE in this table is provided by Saw Palmetto Harvesting Company, Frostproof, FL and has a phytosterol concentration of 0.16 wt.%. The topical vehicle may be chosen appropriate to the use of the preparation as a liquid a gel, a foam, a styling

mousse, a styling hair tonic, a styling hair spray, a pad dampener, other means suitable for application to the scalp. All percentages are by weight.

TABLE I

5

TABLE II

Examples 15-21

Table III below provides examples of preparations of the invention. The SPBE in this table has been purified from the SPBE provided by Saw Palmetto Harvesting Company, Frostproof, FL by extraction with an aqueous alkaline solution and has a phytosterol concentration of 0.5 wt%. The topical vehicle may be chosen appropriate to the use of the preparation as a liquid, a gel, a foam, a styling mousse, a styling hair tonic, a styling hair spray, a pad dampened with a liquid, or any other means suitable for application to the scalp. All percentages are by weight.

Table III

Constituent	Ex. 15	Ex. 16	Ex. 17	Ex. 18	Ex. 19	Ex. 20	Ex. 21
SPBE , %	15.0	20.0	30.0	10.0	10.0	10.0	10.0
adapalene,%	0.05	0.05	-	-	-	-	
glycolic acid, %	5.0	-	1.0	5.0	-	5.0	5.0
tretinoin, %	-	-	0.025		0.1	-	0.05
retinaldehyde,%	-		-	0.1	-	-	
azelaic acid,%	-	-	-	15	10	-	
tazarotene,%	-	-	-	-	-	0.1	
salicylic acid,%	-	2.0	-	-	-	-	
polyol prepolymer-2,%	10	10	10	10	10	10	10
Topical Vehicle	Balance						

CLAIMS

What is claimed is:

1. A low irritability topical preparation for the treatment of hair loss comprising saw palmetto berry extract containing phytosterols and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin gel microsponges, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid.
2. A topical preparation as recited by Claim 1, wherein the penetration enhancing constituents consist of one member selected from the group consisting of adapalene and tretinoin gel microsponges, and another member selected from the group consisting of salicylic acid and glycolic acid.
3. A topical preparation as recited by Claim 1, wherein the penetration enhancing constituents are adapalene and glycolic acid.
4. A topical preparation as recited by Claim 1, wherein the concentration of phytosterols in the preparation ranges from about 0.01 wt.% to about 1 wt.%.
5. A topical preparation as recited by Claim 1, wherein the concentration of phytosterols in the preparation ranges from about 0.01 wt.% to about 0.5 wt.%.
6. A topical preparation as recited by Claim 1, wherein the adapalene concentration ranges from about 0.01 wt.% to about 1 wt.%.
- 20 7. A topical preparation as recited by Claim 1, wherein the glycolic acid concentration ranges from about 0.1 wt.% to about 20 wt.%.
8. A topical preparation as recited by Claim 1, wherein the tretinoin concentration in the form of gel microsponges ranges from about 0.005 wt.% to about 0.2 wt.%.

9. A topical preparation as recited by Claim 1, where the concentration ranges from about 0.01 wt.% to about 1.0 wt.%.

10. A topical preparation as recited by Claim 1, wherein the azelaic acid concentration ranges from about 0.1 wt% to about 40 wt%.

5 11. A topical preparation as recited in Claim 1, wherein the total concentration of azelaic acid and glycolic acid ranges from about 0.1% to about 40%.

12. A topical preparation as recited in Claim 1, wherein the proportion of azelaic acid to glycolic acid ranges from about 10:90 to about 90:10.

10 13. A topical preparation as recited by Claim 1, wherein the tazarotene concentration ranges from about 0.01 wt.% to about 1.0 wt.%.

14. A topical preparation as recited by Claim 1, wherein the salicylic acid concentration ranges from about 0.1 wt.% to about 10 wt.%.

15 15. A topical preparation as recited by Claim 1, wherein the preparation further contains a topical vehicle for application to the scalp selected from the group consisting of liquid, gel, foam, styling mousse, styling hair tonic and styling hair spray.

20 16. A low irritability topical preparation for the prevention of hair loss comprising saw palmetto berry extract containing phytosterols, polyol prepolymer-2 and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid.

25 17. A topical preparation as recited by Claim 16, wherein the penetration enhancing constituents consist of one member selected from the group consisting of adapalene and tretinoin, and another member selected from the group consisting of salicylic acid and glycolic acid.

18. A topical preparation as recited by Claim 16, wherein the penetration enhancing constituents are adapalene and glycolic acid.

5 19. A topical preparation as recited by Claim 16, wherein the preparation contains a topical vehicle for application to the scalp selected from the group consisting of liquid, gel, foam, styling mousse, styling hair tonic and styling hair spray.

10 20. A method for the treatment of male pattern hair loss, comprising applying to the scalp a low irritability preparation comprising saw palmetto berry extract containing phytosterols and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin gel microsponges, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid.

15 21. A method for the prevention of male pattern hair loss, comprising applying to the scalp a low irritability preparation comprising saw palmetto berry extract containing phytosterols, polyol prepolymer-2, and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid.

20 22. A low irritability topical preparation for the treatment of hair loss comprising saw palmetto berry extract containing phytosterols and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin gel microsponges, tretinoin and polyol prepolymer-2, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 November 2001 (08.11.2001)

PCT

(10) International Publication Number
WO 01/82880 A3

(51) International Patent Classification²: **A61K 7/06**

(21) International Application Number: PCT/US01/13900

(22) International Filing Date: 30 April 2001 (30.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/563,555 3 May 2000 (03.05.2000) US

(71) Applicant and
(72) Inventor: GOODMAN, David, S. [US/US]; 721 Wood-havin Lane, Naples, FL 34108 (US).

(74) Agent: PEARLMAN, Robert, I.; Riker, Danzig, Scherer, Hyland & Perretti LLP, Headquarters Plaza, One Speedwell Avenue, Morristown, NJ 07962 (US).

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:
4 April 2002

Date of publication of the amended claims and statement:
23 May 2002

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/82880 A3

(54) Title: TOPICAL PREPARATION FOR THE TREATMENT OF HAIR LOSS

(57) Abstract: Improved preparations for the treatment of androgenetic alopecia comprise saw palmetto berry extract containing phytosterols and one or more low irritability constituents that enhance penetration of the extract into hair follicular pores. The low irritability penetration enhancer(s) may be selected from the group consisting of adapalene, tretinoin, retinaldehyde, tazarotene, salicylic acid, azelaic acid, and glycolic acid. Also provided is a method for reducing hair loss by application to the scalp of the improved preparations.

AMENDED CLAIMS

[received by the International Bureau on 23 January 2002 (23.01.02);
original claims 1-22 cancelled; new claims 23-40 added (3 pages)]

23. A low irritability topical preparation for the treatment of hair loss comprising:

- (A) saw palmetto berry alcohol extract containing phytosterols;
- (B) one or more members of the group consisting of adapalene, retinaldehyde, tazarotene, salicylic acid, glycolic acid and azelaic acid; and
- (C) polyol prepolymer-2.

24. A topical preparation according to claim 23 comprising salicylic acid or glycolic acid together with adapalene and further comprising tretinoin gel microsponges..

25. A topical preparation according to claim 23 containing the combination of adapalene and glycolic acid.

26. A topical preparation according to claim 23 containing polyol prepolymer-2 and a member of the group consisting of salicylic acid and glycolic acid.

27. The preparation of claim 23 which further comprises a member of the group consisting of tretinoin and tretinoin gel microsponges.

28. A topical preparation as recited by Claim 23, wherein the concentration of phytosterols in the preparation ranges from about 0.01 wt.% to about 1 wt.%.

29. A topical preparation as recited by Claim 23, wherein the concentration of phytosterols in the preparation ranges from about 0.01 wt.% to about 0.5 wt.%.

30. A topical preparation as recited by Claim 23, wherein the adapalene concentration ranges from about 0.01 wt.% to about 1 wt.%.

31. A topical preparation as recited by Claim 23, wherein the glycolic acid concentration ranges from about 0.1 wt.% to about 20 wt.%.

32. A topical preparation as recited by Claim 23, wherein the tretinoin concentration in the form of gel microsponges ranges from about 0.005 wt.% to about 0.2 wt.%.

33. A topical preparation as recited by Claim 23, wherein the retinaldehyde concentration ranges from about 0.01 wt.% to about 1.0 wt.%.

34. A topical preparation as recited by Claim 23, wherein the azelaic acid concentration ranges from about 0.1 wt% to about 40 wt%.

35. A topical preparation as recited in Claim 23, wherein the total concentration of azelaic acid and glycolic acid ranges from about 0.1% to about 40%.

36. A topical preparation as recited in Claim 23, wherein the proportion of azelaic acid to glycolic acid ranges from about 10:90 to about 90:10.

37. A topical preparation as recited by Claim 23, wherein the tazarotene concentration ranges from about 0.01 wt.% to about 1.0 wt.%.

38. A topical preparation as recited by Claim 23, wherein the salicylic acid concentration ranges from about 0.1 wt.% to about 10 wt.%.

39. A topical preparation as recited by Claim 23, wherein the preparation contains a topical vehicle for application to the scalp selected from the group consisting of liquid, gel, foam, styling mousse, styling hair tonic and styling hair spray.

40. A method for the treatment of male pattern hair loss, comprising applying to the scalp a low irritability preparation comprising saw palmetto berry alcohol extract containing phytosterols; and one or more penetration enhancing constituents selected from the group consisting of adapalene, tretinoin retinaldehyde,

tazarotene, salicylic acid, azelaic acid, and glycolic acid; prepolymer-2 and, optionally tretinoin gel microsponges.

STATEMENT UNDER ARTICLE 19(1)

The following amendments to the claims in this patent application.

Originally claims 1-22 are hereby cancelled and replaced by new claims 23-40. The new claims correspond to those allowed in the corresponding U.S. Patent Application and patentably distinguish over the cited prior art.